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Term: L9 same l3

Display: 10 **Documents in Display Format:** - **Starting with Number** 1

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Search History

DATE: Wednesday, May 25, 2005 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L10	L9 same l3	14	L10
L9	L8 same l7	1219	L9
L8	mutation or dele$	376038	L8
L7	e1a with adeno$	2848	L7
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L6	L5 with L4	45	L6
L5	tissue specific or tumor specific	31386	L5
L4	replication competent with adenovi$	954	L4
L3	L2 with L1	75	L3
L2	vector or adenovir$	355457	L2
L1	E2F with promoter	320	L1

END OF SEARCH HISTORY

L6: Entry 3 of 45 File: PGPB Jan 6, 2005

DOCUMENT-IDENTIFIER: US 20050002906 A1
TITLE: Gene therapy using replication competent targeted adenoviral vectors

Abstract Paragraph:
This invention provides a method of treating cancer by administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene. The replication competent targeted adenoviral vector preferentially replicates in the tumor cells following activation of the tumor specific gene regulatory region thereby amplifying the effect of the therapeutic gene carried by the replication competent adenoviral vector. This invention enables for the first time the targeting of a therapeutic gene for treating cancer using small amounts of viral vectors which selectively replicate to deliver therapeutic dosages of the therapeutic gene.

Summary of Invention Paragraph:
[0011] This invention provides a method of treating cancer by administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene. The replication competent targeted adenoviral vector preferentially replicates in the tumor cells following activation of the tumor specific gene regulatory region thereby amplifying the effect of the therapeutic gene carried by the replication competent adenoviral vector. This invention enables for the first time the targeting of a therapeutic gene for treating cancer using small amounts of viral vectors which selectively replicate to deliver therapeutic dosages of the therapeutic gene.

Detail Description Paragraph:
[0016] In one embodiment, the invention is directed to the therapeutic use of engineered replication competent recombinant adenoviruses to treat cancer and other hyperproliferative disorders or diseases in which there is a unique factor substance which would allow targeted delivery of a therapeutic substance using the method of this invention. The viruses have been modified to reduce their ability to replicate in normal cells while retaining their ability to replicate efficiently in specific tumor types. The adenoviral vectors include therapeutic genes such as cytotoxic genes or tumor suppressor genes which are lethal or otherwise render the cancer non-malignant or anti-sense compounds to certain viruses such as hepatitis or cytomegalovirus, or anti-viral compounds such as interferon-alpha. The tumor specific replication competent vectors have been engineered such that the promoter of the adenoviral E1a gene has been replaced with a tumor specific promoter/enhancer. An important distinction between these recombinant viruses and those typically used for gene therapy is that a replication gene such as the E1 gene, themselves are retained in the resulting recombinant adenoviruses. Because the viral E1 gene controls transcription of many other important viral genes (Horowitz, 1990) this modification restricts virus replication to those tumors which utilize the tumor specific promoter/enhancer inserted in place of the E1a promoter. One example of a cytotoxic gene is the Herpes simplex type-1 thymidine kinase gene which itself has a selective toxicity to replicating cells in the presence of the drug ganciclovir (F. L. Moolten, 1986). Replication of the recombinant adenovirus within the tumor mass amplifies the effect of the cytotoxic

gene carried by the virus.

CLAIMS:

1. A method of treating mammalian cancer cells, comprising administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene wherein the cancer cells activate the tumor specific gene regulatory region causing the adenoviral vector to replicate.

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L6: Entry 25 of 45 File: PGPB Feb 6, 2003

DOCUMENT-IDENTIFIER: US 20030026789 A1
TITLE: GENE THERAPY USING REPLICATION COMPETENT TARGETED ADENOVIRAL VECTORS

Abstract Paragraph:
This invention provides a method of treating cancer by administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene. The replication competent targeted adenoviral vector preferentially replicates in the tumor cells following activation of the tumor specific gene regulatory region thereby amplifying the effect of the therapeutic gene carried by the replication competent adenoviral vector. This invention enables for the first time the targeting of a therapeutic gene for treating cancer using small amounts of viral vectors which selectively replicate to deliver therapeutic dosages of the therapeutic gene.

Summary of Invention Paragraph:
[0011] This invention provides a method of treating cancer by administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene. The replication competent targeted adenoviral vector preferentially replicates in the tumor cells following activation of the tumor specific gene regulatory region thereby amplifying the effect of the therapeutic gene carried by the replication competent adenoviral vector. This invention enables for the first time the targeting of a therapeutic gene for treating cancer using small amounts of viral vectors which selectively replicate to deliver therapeutic dosages of the therapeutic gene.

Detail Description Paragraph:
[0016] In one embodiment, the invention is directed to the therapeutic use of engineered replication competent recombinant adenoviruses to treat cancer and other hyperproliferative disorders or diseases in which there is a unique factor substance which would allow targeted delivery of a therapeutic substance using the method of this invention. The viruses have been modified to reduce their ability to replicate in normal cells while retaining their ability to replicate efficiently in specific tumor types. The adenoviral vectors include therapeutic genes such as cytotoxic genes or tumor suppressor genes which are lethal or otherwise render the cancer non-malignant or anti-sense compounds to certain viruses such as hepatitis or cytomegalovirus, or anti-viral compounds such as interferon-alpha. The tumor specific replication competent vectors have been engineered such that the promoter of the adenoviral E1a gene has been replaced with a tumor specific promoter/enhancer. An important distinction between these recombinant viruses and those typically used for gene therapy is that a replication gene such as the E1 gene, themselves are retained in the resulting recombinant adenoviruses. Because the viral E1 gene controls transcription of many other important viral genes (Horowitz, 1990) this modification restricts virus replication to those tumors which utilize the tumor specific promoter/enhancer inserted in place of the E1a promoter. One example of a cytotoxic gene is the Herpes simplex type-1 thymidine kinase gene which itself has a selective toxicity to replicating cells in the presence of the drug ganciclovir (F. L. Moolten, 1986). Replication of the recombinant adenovirus within the tumor mass amplifies the effect of the cytotoxic

gene carried by the virus.

CLAIMS:

1. A method of treating mammalian cancer cells, comprising administering a replication competent adenoviral vector comprising a therapeutic gene and a disease specific gene regulatory region operationally linked to at least one replication gene wherein the cancer cells activate the tumor specific gene regulatory region causing the adenoviral vector to replicate.

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L6: Entry 27 of 45 File: PGPB Oct 3, 2002

DOCUMENT-IDENTIFIER: US 20020142989 A1
TITLE: Oncolytic/immunogenic complementary-adenoviral vector system

Summary of Invention Paragraph:
[0028] The .alpha.-fetoprotein (AFP) promoter/enhancer cassettes have been utilized to control E1 expression from an Ad vector in order to induce a virus-mediated oncolytic effect on hepatocellular carcinoma (Hallenbeck et al., 1996). As proof of concept for the first generation of a tumor specific replication competent adenoviral (TSRCA) vector, the Ad5 E1 promoter of a wild-type Ad was replaced with a modified version of the AFP promoter. The vectors were shown to replicate in two-thirds of human hepatocellular carcinoma cell lines tested that expressed high levels of AFP. Furthermore, approximately 500-1000 hepatocellular carcinoma cells per virion particle were destroyed in a 13 day assay. Little to no replication was observed in two liver cell lines, two lung cancer cell lines, one colon cancer cell line, and one cervical cancer cell line, each of which do not produce AFP. In addition, investigators tested two primary cultures of normal human lung epithelial and endothelial cells for replication of the vectors since lung tissue is the primary target for Ad replication in human. Neither primary culture supported replication of the vectors, demonstrating the specificity of the vectors in cancer cell killing (Hallenbeck et al., 1996). The investigators also proposed the use of other tumor-specific promoter/enhancers of different cancers using the same type of design as the TSRCA vector.

Detail Description Paragraph:
[0169] Hallenbeck, P. L., Chang, Y-N., Hay, C., Golightly, D., Stewart, D., McGarrity, G. & Chiang, Y. (1996) Novel tumor specific replication competent adenoviral vectors for gene therapy of cancer. Cancer Gene Ther., vol. 3, pp. S19-20.

First Hit Previous Doc Next Doc Go to Doc#

Generate Collection Print

L10: Entry 2 of 14 File: PGPB Dec 2, 2004

DOCUMENT-IDENTIFIER: US 20040241142 A1
TITLE: Oncolytic adenovirus

Detail Description Paragraph:
[0093] One embodiment of the invention is the description of an adenovirus Ela and/or E4 shuttle vector that allows fast and easy substitution of the endogenous nucleotide transcriptional regulatory sequences, where such sequences are preferably Ela and/or E4 promoter sequences, with nucleotide transcriptional regulatory sequences that are response to elements (i.e. molecules) in the pRb signaling pathway, including pRb/p107, E2F transcription factors such as E2F-1/-2/-3, and G1 cyclin/cdk complexes. An E1a or E4 adenoviral vector, as described above, would be expected to be attenuated in normal cells that contain an intact, that is wild type pRb pathway, yet exhibit a normal infection profile in cells that are deficient in Rb pathway function, including for pRb's repressive function. Due to the presence of the autoregulatory E2F sites in the E2F-1 promoter, any E1A or E4 adenoviral vector having nucleotide transcriptional regulatory sequences that are response to elements in the pRb signaling pathway substituted for the endogenous E1a and/or E4 sequences will preferably have a second mutation in the E1A-CR2 (conserved region 2) domain. This is desirable to minimize E1A's ability to disrupt pRb-mediated repression of the E2F elements.

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L10: Entry 2 of 14 File: PGPB Dec 2, 2004

PGPUB-DOCUMENT-NUMBER: 20040241142
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040241142 A1

TITLE: Oncolytic adenovirus

PUBLICATION-DATE: December 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Johnson, Leisa	Richmond	CA	US	
Fattaey, Ali	Oakland	CA	US	
Hermiston, Terry	Corte Madera	CA	US	
Shen, Jerry Yuqiao	Orinda	CA	US	
Laquerre, Sylvie	Conshohocken	PA	US	

APPL-NO: 10/ 733674 [PALM]
DATE FILED: December 11, 2003

RELATED-US-APPL-DATA:
Application 10/733674 is a continuation-in-part-of US application 10/303598, filed November 25, 2002, PENDING
Application 10/303598 is a continuation-in-part-of US application 09/714409, filed November 14, 2000, PENDING
Application is a non-provisional-of-provisional application 60/165638, filed November 15, 1999,

INT-CL: [07] A61 K 48/00, C12 N 7/00, C12 N 15/861

US-CL-PUBLISHED: 424/093.2; 435/235.1, 435/456
US-CL-CURRENT: 424/93.2; 435/235.1, 435/456

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

Viral vectors and methods of making such vectors are described that preferentially kill neoplastic but not normal cells, the preferred vector being an adenovirus that has the endogenous promoters in the E1A and/or E4 regions substituted with a tumor specific promoter which is preferably E2F responsive.

FIELD OF THE INVENTION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 10/303,598 filed Nov. 25, 2002, which is a continuation-in-part of U.S. patent application Ser. No. 09/714,409 filed Nov. 14, 2000, which in turn claims priority

from U.S. Provisional Application No. 60/165,638, filed Nov. 15, 1999.

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L10: Entry 7 of 14 File: PGPB Oct 17, 2002

DOCUMENT-IDENTIFIER: US 20020150557 A1
TITLE: Selectively replicating viral vectors

Detail Description Paragraph:
[0040] For example, the selectively replicating adenoviral vectors U3EE and T1LT are designed to achieve selective replication and killing of tumor cells having p53 pathway defects. The U3EE is prepared in substantial accordance with the teaching of Examples herein. Briefly, the U3EE virus contains a first expression cassette comprising a p53 response element (p53 CON) driving expression of the E2F-Rb fusion protein. The E2F-Rb fusion protein is a potent inhibitor of adenoviral E2 promoter activity and its presence in the cell will effectively suppress viral replication. The p53 response element is active in response to the presence of a functional p53 pathway. Consequently, in normal cells where the p53 pathway is intact, the U3EE virus will express the E2F-Rb fusion protein and the virus will not replicate. However, in cells having p53 pathway defect (the majority of tumor cells), the p53CON response element is not active and thus there is no repression of viral replication. The U3EE vector also contains an expression cassette comprising the MLP promoter driving expression of the AdS E3-10.5K pro-apoptotic gene. The use of the temporal promoters (such as the MLP promoter) is preferred when employing pro-apoptotic genes because one wishes to facilitate replication of viral DNA within the target cell prior to activating the pro-apoptotic signal. The MLP promoter is activated approximately seven hours post-infection following onset if replication of the U3EE genome thus inducing the activity of the E3-10.5 K protein. The T1LT adenoviral vector is essentially the same as the U3EE vector except that it contains an additional deletion in the E1a region to removes amino acids 4-25 of the 243R and 289R adenoviral E1a proteins. This deletion disrupts the ability of the p300 protein to bind to these E1a proteins.

Detail Description Paragraph:
[0095] A particularly preferred embodiment of the invention is the selectively replicating adenoviral vector designated 01/PEME which is a recombinant adenoviral vector which been modified in accordance with the teaching of the present invention and incorporates several of the features described herein: 1) a deletion in the E1a gene corresponding to amino acids 4-25 of the E1a 243R and 289R proteins (dl1101) that prevents viral inactivation of p53 and viral induction of cellular DNA synthesis synthesis (Howe, et al. (1990) PNAS(USA) 87:5883-7.), 2) a deletion in the E3 region derived from dl327 that prevents viral interference with immune response Andersson M, et al. (1985) Cell 43:215-22, and Burgert, et al. (1987) PNAS (USA) 84:1356-60)3) an expression cassette comprising the PRP promoter expressing the E2F-RB fusion protein (PRP-E2F-Rb, Gregory et al. supra)that blocks viral replication in normal cells, and 4) insertion of a modified viral gene expression cassette wherein the E311.6K protein is under control of the adenovirus type 5 major late promoter (MLP-E3-11.6K) to enhances virus spread in tumor cells (Tollefson, et al. (1996) Virology 220:152-62 and Tollefson, et al. 1996) J. Virol. 70:2296-306.) In cells in which growth and apoptosis are dysregulated, hallmarks of neoplastic transformation, expression of the inhibitor, E2F-Rb, is blocked and replication of 01/PEME proceeds with efficiencies similar to those of wild type adenovirus. In normal cells, including actively dividing cells, the inhibitor is expressed and viral replication is effectively prevented. In data which is presented in more detail below, when tested in vitro against a panel of 31 tumor

cell lines and 4 normal primary cell cultures 01/PEME was highly selective for tumor cells versus normal cells. In mouse models, 01/PEME administered by intravenous administration was effective against established human xenograft tumors derived from lung, colorectal, prostate and cervical carcinomas.

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L10: Entry 10 of 14 File: USPT Oct 26, 1999

US-PAT-NO: 5972706
DOCUMENT-IDENTIFIER: US 5972706 A

TITLE: Cytopathic viruses for therapy and prophylaxis of neoplasia

DATE-ISSUED: October 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McCormick; Francis	Richmond	CA		

US-CL-CURRENT: 435/440; 424/93.2, 424/93.3, 424/93.6, 435/235.1, 435/236, 435/320.1, 514/44

CLAIMS:

I claim:

1. A method for ablating cells that lack a functional Rb tumor suppressor gene product from a population of cells, comprising the steps of:

contacting under infective conditions (1) a recombinant replication deficient adenovirus substantially lacking an expressed viral oncoprotein capable of binding a functional Rb tumor suppressor gene product, with (2) said cell population comprising neoplastic cells that lack functional Rb, non-neoplastic cells that have functional Rb, and non-neoplastic cells that transiently lack Rb, wherein said functional Rb tumor suppressor gene product forms a bound complex with said viral oncoprotein, and (3) allowing sufficient time for said adenovirus to ablate said neoplastic and non-neoplastic cells that lack said functional Rb tumor suppressor gene product.

2. A method according to claim 1, wherein the viral oncoprotein is an adenovirus E1a polypeptide.

3. A method according to claim 2, wherein the viral oncoprotein is an adenovirus E1a polypeptide, said E1a polypeptide having mutations in the E1a CR1 domain (amino acids 30-85 in Ad5: nucleotide positions 697-790) and/or the CR2 domain (amino acids 120-139 in Ad5; nucleotide positions 920-967).

4. A method according to claim 3, wherein the recombinant replication deficient adenovirus is selected from the group consisting of Ad5 NT dl 1010 and Ad5 dl 312.

5. A method according to claim 1, wherein said cell population comprising neoplastic cells and non-neoplastic cells is present in a mammal and said contacting step is performed in vivo by administering the recombinant replication deficient adenovirus to said mammal.

6. A method according to claim 5, wherein the mammal is a human.

7. A method according to claim 1, wherein the recombinant replication deficient adenovirus can be replicated to form infectious virions in a neoplastic cell lacking RB function.

8. A method according to claim 7, wherein the infectious virions formed in the neoplastic cell are able to spread and infect adjacent cells in vivo in a patient.

9. A method according to claim 1, wherein the recombinant replication deficient adenovirus is an E1a/E1b double mutant.

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     (FILE 'HOME' ENTERED AT 14:00:06 ON 25 MAY 2005)

     FILE 'MEDLINE, CANCERLIT' ENTERED AT 14:00:32 ON 25 MAY 2005
L1           213 S ONYX
L2            19 S L1 AND REVIEW
L3            15 DUP REM L2 (4 DUPLICATES REMOVED)
L4         43144 S ADENOV?
L5           329 S E2F AND BINDING SITE
L6            71 S L5 AND L4
L7            39 DUP REM L6 (32 DUPLICATES REMOVED)
L8          5961 S E1A
L9            30 S L8 AND L7
L10      2877876 S CANCER OR TUMOR OR NEOPLAS?
L11           11 S L10 AND L9

     FILE 'MEDLINE, CANCERLIT, EMBASE, BIOSIS, CAPLUS, BIOTECHDS' ENTERED AT
     14:30:15 ON 25 MAY 2005
L12           30 S L8 AND L7
L13      5958036 S L10
L14          136 S L5 AND L4 AND L8
L15           44 S L14 AND L13
L16           23 DUP REM L15 (21 DUPLICATES REMOVED)

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L16 ANSWER 8 OF 23 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 1999290271 EMBASE
TI The **adenovirus** oncoprotein **E1a** stimulates binding of transcription factor ETF to transcriptionally activate the p53 gene.
AU Hale T.K.; Braithwaite A.W.
CS T.K. Hale, Department of Pathology, Dunedin School of Medicine, University of Otago, P.O. Box 913, Dunedin 9000, New Zealand.
tracy.hale@stonebow.otago.ac.nz
SO Journal of Biological Chemistry, (20 Aug 1999) Vol. 274, No. 34, pp. 23777-23786.
Refs: 83
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 004 Microbiology
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 19990903
Last Updated on STN: 19990903
AB Expression of the **tumor** suppressor protein p53 plays an important role in regulating the cellular response to DNA damage. During **adenovirus** infection, levels of p53 protein also increase. It has been shown that this increase is due not only to increased stability of the p53 protein but to the transcriptional activation of the p53 gene during infection. We demonstrate here that the **E1a** proteins of **adenovirus** are responsible for activating the mouse p53 gene and that both major **E1a** proteins, 243R and 289R, are required for complete activation. **E1a** brings about the binding of two cellular transcription factors to the mouse p53 promoter. One of these, ETF, binds to three upstream sites in the p53 promoter and one downstream site, whereas **E2F** binds to one upstream site in the presence of **E1a**. Our studies indicate that **E2F** binding is not essential for activation of the p53 promoter but that ETF is. Our data indicate the ETF site located downstream of the start site of transcription is the key site in conferring **E1a** responsiveness on the p53 promoter.

L16 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:507868 CAPLUS
DN 135:103355
TI **Cancer** cell-specific gene expression system containing binding sites for **E2F** transcription factor (E2Fbs)
IN Yeom, Young Il; Lim, Mi Jung; Han, Jung Hee; Lim, Jong Seok; Kim, Kwang Dong; Kim, Chang Kyu
PA Korea Research Institute of Bioscience and Biotechnology, S. Korea; Chong Kun Dang Pharmaceutical Corporation
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001049868	A1	20010712	WO 2000-KR330	20000410
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	KR 2001069182	A	20010723	KR 2000-18415	20000408
	AU 2000041472	A5	20010716	AU 2000-41472	20000410
PRAI	KR 1999-68205	A	19991231		
	WO 2000-KR330	W	20000410		

AB The present invention relates to a **cancer**-specific gene expression system, more particularly to a **cancer**-specific gene expression system characterized comprising a promoter with a **binding site** (E2Fbs) for **E2F** transcription factor expressed only in cancerous cells. Several plasmid vector were constructed and the transcriptional activity of E2Fbs was tested in the presence of oncoprotein **E1A** or E7 in normal cells. The transcriptional activity of E2Fbs was also tested in several cell lines, including COS-7, Hela, 293, Saos-2, Caski and C3 cells. The cytotoxic activity of the E2Fbs-containing plasmid encoding a therapeutic gene was evaluated. The gene expression system thus can provide an effective way in conjunction with various combined structural genes to treat **cancer** by using the special feature of the vector that specifically works on cancerous cells without affecting any nor

upstream sequences. (25 pages)

L16 ANSWER 2 OF 23 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003136097 EMBASE
TI An oncolytic **adenovirus** selective for retinoblastoma **tumor** suppressor protein pathway-defective tumors: Dependence on **E1A**, the **E2F**-1 promoter, and viral replication for selectivity and efficacy.
AU Jakubczak J.L.; Ryan P.; Gorziglia M.; Clarke L.; Hawkins L.K.; Hay C.; Huang Y.; Kaloss M.; Marinov A.; Phipps S.; Pinkstaff A.; Shirley P.; Skripchenko Y.; Stewart D.; Forry-Schaudies S.; Hallenbeck P.L.
CS P.L. Hallenbeck, Genetic Therapy, Inc., 45 West Watkins Mill Road, Gaithersburg, MD 20878, United States. paul.hallenbeck@pharma.novartis.com
SO Cancer Research, (1 Apr 2003) Vol. 63, No. 7, pp. 1490-1499.
Refs: 55
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 004 Microbiology
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20030424
Last Updated on STN: 20030424
AB The use of oncolytic **adenoviruses** as a **cancer** therapeutic is dependent on the lytic properties of the viral life cycle, and the molecular differences between **tumor** cells and nontumor cells. One strategy for achieving safe and efficacious **adenoviral** therapies is to control expression of viral early gene(s) required for replication with **tumor**-selective promoter(s), particularly those active in a broad range of **cancer** cells. The retinoblastoma **tumor** suppressor protein (Rb) pathway is dysregulated in a majority of human cancers. The human **E2F**-1 promoter has been shown to be selectively activated/derepressed in **tumor** cells with a defect in the Rb pathway. Ar6pAE2fE3F and Ar6pAE2fF are oncolytic **adenoviral** vectors (with and without the viral E3 region, respectively) that use the **tumor**-selective **E2F**-1 promoter to limit expression of the viral **E1A** transcription unit, and, thus, replication, to **tumor** cells. We demonstrate that the antitumor activity of Ar6pAE2fF in vitro and in vivo is dependent on the **E2F**-1 promoter driving **E1A** expression in Rb pathway-defective cells, and furthermore, that its oncolytic activity is enhanced by viral replication. Selective oncolysis by Ar6pAE2fF was dependent on the presence of functional **E2F** binding sites in the **E2F**-1 promoter, thus linking antitumor viral activity to the Rb pathway. Potent antitumor efficacy was demonstrated with Ar6pAE2fF and Ar6pAE2fE3F in a xenograft model following intratumoral administration. Ar6pAE2fF and Ar6pAE2fE3F were compared with Add/1520, which is reported to be molecularly identical to an E1B-55K deleted vector currently in clinical trials. These vectors were compared in in vitro cytotoxicity and virus production assays, after systemic delivery in an in vivo **E1A** -related hepatotoxicity model, and in a mouse xenograft **tumor** model after intratumoral administration. Our results support the use of oncolytic **adenoviruses** using **tumor**-selective promoter(s) that are activated or derepressed in **tumor** cells by virtue of a particular defective pathway, such as the Rb pathway.

L3 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 1
AN 2002162110 MEDLINE
DN PubMed ID: 11894142
TI Replication-selective viruses for cancer therapy.
AU Biederer Carola; Ries Stefan; Brandts Christian H; McCormick Frank
CS SWITCH Biotech AG, Fraunhofer Strasse 10, 82152 Martinsried, Germany.
SO Journal of molecular medicine (Berlin, Germany), (2002 Mar) 80 (3) 163-75.
Electronic Publication: 2001-12-20. Ref: 113
Journal code: 9504370. ISSN: 0946-2716.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020315
Last Updated on STN: 20030105
Entered Medline: 20020830
AB Advances in our understanding of the molecular basis of cancer and the availability of technology to genetically engineer viruses have led to the development of replication-competent viruses to treat cancer. In theory, replication-selective viruses offer several appealing properties as biological agents for cancer therapy: they kill tumor cells selectively, and their replication leads to amplification of their oncolytic potential. Most preclinical experiments in tissue culture and in animal models support this notion. Clinical data on the first generation of replication-selective viruses are now rapidly accruing. The therapeutic index, and ultimately the clinical outcome, will depend on a complex balance between host and viral factors. This **review** discusses strategies to kill cancer cells based on our understanding of their molecular defects and the progress being made using replication-competent viruses for tumor therapy. We focus our discussion on a replication-selective adenovirus called **ONYX**-015 that has recently demonstrated encouraging results in clinical trials

L3 ANSWER 11 OF 15 MEDLINE on STN
AN 2002683084 MEDLINE
DN PubMed ID: 12444391
TI Understanding the biology of oral cancer.
AU Das Bibhu R; Nagpal Jatin K
CS Molecular Oncology and Medical Biotechnology Division, Institute of Life Sciences, Chandrasekharpur, Bhubaneswar, India.. brdils@hotmail.com
SO Medical science monitor : international medical journal of experimental and clinical research, (2002 Nov) 8 (11) RA258-67. Ref: 115
Journal code: 9609063. ISSN: 1234-1010.
CY Poland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20021122
Last Updated on STN: 20030529
Entered Medline: 20030528
AB The present **review** is an attempt to summarize the important advances made during the last decade in the molecular approach to oral cancer and its application for early, sensitive diagnosis, effective treatment, and improved prognosis. Cancer of the oral cavity is more prevalent in developing countries, where many people are addicted to tobacco chewing and maintain poor oral hygiene. Despite extensive research on the biological and molecular aspects of oral SCC, the problems of local-regional recurrence and distant metastasis still persist. Among the more pressing problems in clinical management is the lack of early detection, due to the absence of a potential diagnostic marker. Oncologists are now more aware of the challenges associated with the treatment of cancer of the oral cavity, and survival percentages are improving significantly. More trials are need in the area of improved surgical procedures, variations in dosages of radiotherapy, and the use of various combinations of chemotherapeutic agents with minimal side effects. Moreover, progress in the elucidation of the molecular genetic changes that lead to the development of these tumors should soon bring novel diagnostic and therapeutic procedures into clinical practice. The case of **ONYX**-015 is one example of success, which has shown the great potential in Phase-I and II clinical trials. Finally, the legislator should also impose some restrictions and bans on the easy availability of various forms of tobacco.

L3 ANSWER 10 OF 15 MEDLINE on STN
AN 2002176110 MEDLINE
DN PubMed ID: 11890870
TI Head and neck cancer: gene therapy approaches. Part II: genes delivered.
AU Nemunaitis John; O'Brien John
CS 3535 Worth Street, Collins Building, 5th Floor, Dallas, Texas 75246, USA..
John.Nemunaitis@USOncology.com
SO Expert opinion on biological therapy, (2002 Mar) 2 (3) 311-24. Ref: 209
Journal code: 101125414. ISSN: 1471-2598.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20020324
Last Updated on STN: 20030116
Entered Medline: 20030115
AB In Part I, the **review** summarised the safety of adenoviral vectors and provided insight into approaches being undertaken to improve the specificity, durability and potency of adenoviral delivery vehicles. In Part II, brief discussions are held regarding results of preclinical and clinical trials with a variety of different genes, which have demonstrated antitumour activity in squamous cell carcinoma of the head and neck region (HNSCC). Studies have been performed with a variety of immune modulatory genes. Preliminary results demonstrate activity with several cytokine genes, tumour antigen genes and co-stimulatory molecule genes. Despite only preliminary results, thus far, a theoretical attractive feature for the use of gene therapy for the enhancement of immune modulation is that local injection of the gene product appears to be well tolerated. It is also successful in inducing systemic immune response, potentially providing effect to metastatic sites distal from the injected site. Animal studies have confirmed efficacy in the use of specific targeting of molecules regulating cancer growth (EGF receptor [EGFR], super oxide dismutase [SOD], cyclin D1, E1A and Bcl-2). These approaches are discussed. However, the most significant clinical advances for the use of gene therapy in advanced HNSCC involves two agents: Adp53 and **ONYX**-015. Preliminary Phase I and II results suggest evidence of efficacy and justify accrual Phase III trials, which are currently ongoing.

L3 ANSWER 8 OF 15 MEDLINE on STN
AN 2003015577 MEDLINE
DN PubMed ID: 12522437
TI Intravascular adenoviral agents in cancer patients: lessons from clinical trials.
AU Reid Tony; Warren Robert; Kirn David
CS Stanford University, Palo Alto Veterans Administration Hospital, Palo Alto, California, USA.
SO Cancer gene therapy, (2002 Dec) 9 (12) 979-86. Ref: 52
Journal code: 9432230. ISSN: 0929-1903.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030111
Last Updated on STN: 20030614
Entered Medline: 20030613
AB A large number of adenoviral agents are being developed for the treatment of cancer. However, the treatment-related death of a patient with ornithine transcarbamylase deficiency following adenovirus administration by hepatic artery has led to serious concerns regarding the safety of intravascular adenovirus. Both replication-incompetent (rAd.p53, e.g., SCH58500) and replication-selective (dl1520, aka **Onyx**-015; CG7870) oncolytic adenoviruses, by intravascular administration, are in clinical trials. We **review** Phases I and I/II results from these clinical trials. dl1520 and rAd.p53 were well-tolerated following hepatic artery infusion at doses of up to 2x10(12) and 2.5x10(13) particles, respectively. At a dose of 7.5x10(13) particles, rAd.p53 was associated with dose-limiting cardiac output suppression; dl1520 dose escalation did not proceed higher than 2x10(12). Intravenous (i.v.) infusions of dl1520 and CG7870 have been well tolerated by i.v. infusion at doses of 2x10(13) and 6x10(12), respectively, without identification of a maximally tolerated dose to date. Mild/moderate transaminitis was demonstrated in some patients on both the hepatic arterial and i.v. trials at doses >or=10(12) particles. Interleukin (IL)-6 and IL-10 were induced in a dose-dependent manner in most patients, but significant interpatient and intrapatient (on repeat doses) variabilities were demonstrated. Evidence of p53 gene expression (Ad.p53) or viral replication (dl1520) was demonstrated in the majority of patients receiving >or=10(12) particles. Over 100 cancer patients have been treated with intravascular adenovirus constructs to date with an acceptable toxicity profile; further clinical trial testing appears appropriate in cancer patients.

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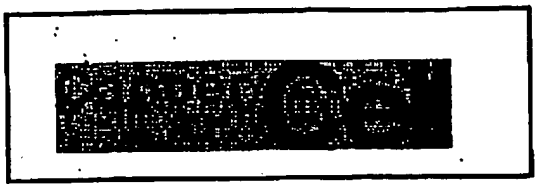

Cancer Cell, Vol 1, 325-337, May 2002

Selectively replicating adenoviruses targeting deregulated E2F activity are potent, systemic antitumor agents

Leisa Johnson [14], Annie Shen [1], Larry Boyle [1], John Kunich [1], Kusum Pandey [1], Marilyn Lemmon [1], Terry Hermiston [16], Marty Giedlin [17], Frank McCormick [2] and Ali Fattaey [15]

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Summary

Summary Significance Introduction Results Discussion Experimental procedures Referenc

We have engineered a human adenovirus, ONYX-411, that selectively replicates in human tumor cel but not normal cells, depending upon the status of their retinoblastoma tumor suppressor protein (pR pathway. Early and late viral gene expression as well as DNA replication were significantly reduced functional pRB-pathway-dependent manner, resulting in a restricted replication profile similar to tha nonreplicating adenoviruses in normal cells both in vitro and in vivo. In contrast, the viral life cycle tumor cell killing activity of ONYX-411 was comparable to that of wild-type adenovirus following infection of human tumor cells in vitro as well as after systemic administration in tumor-bearing animals.

Significance

Summary Significance Introduction Results Discussion Experimental procedures Referenc